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The binding affinity of human IgG for its high affinity Fc receptor is determined by multiple amino acids in the CH2 domain and is modulated by the hinge region.

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A family of chimeric immunoglobulins (Igs) bearing the murine variable region directed against the hapten dansyl linked to human IgG1, -2, -3, and -4 has been characterized with respect to binding to the human high affinity Fc gamma receptor, Fc gamma RI. Chimeric IgG1 and -3 have the highest affinity association (Ka = 10(9) M-1), IgG4 is 10-fold reduced from this level, and IgG2 displays no detectable binding. A series of genetic manipulations was undertaken in which domains from the strongly binding subclass IgG3 were exchanged with domains from the nonbinding subclass IgG2. The subclass of the CH2 domain was found to be critical for determining IgG receptor affinity. In addition, the hinge region was found to modulate the affinity of the IgG for Fc gamma RI, possibly by determining accessibility of Fc gamma RI to the binding site on Fc. A series of amino acid substitutions were engineered into the CH2 domain of IgG3 and IgG4 at sites considered potentially important to Fc receptor binding based on homology comparisons of binding and nonbinding IgG subclasses. Characterization of these mutants has revealed the importance for Fc gamma RI association of two regions of the genetic CH2 domain separated in primary structure by nearly 100 residues. The first of these is the hinge-link or lower hinge regions, in which two residues, Leu (234) and Leu(235) in IgG1 and -3, are critical to high affinity binding. Substitution at either of these sites reduces the IgG association constant by 10-100-fold. The second region that appears to contribute to receptor binding is in a hinge-proximal bend between two beta strands within the CH2 domain, specifically, Pro(331) in IgG1 and -3. As a result of beta sheet formation within this domain, this residue lies within 11 A of the hinge-link region. Substitution at this site reduces the Fc receptor association constant by 10-fold.

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